into said cell, wherein said introduction reverses drug resistance in said cell.

22. A formulation for reversing drug resistance in a cancer cell or inducing apoptosis in a cancer cell, comprising a full length antisense glucosylceramide synthase nucleic acid sequence and chemosensitizer or chemotherapeutic agent.

REMARKS

Claims 1, 3-8, 10-15, 17-19 are pending in this application. Claims 1, 3-8, 10-15, 17-19 stand rejected. New claims 21 and 22 have been added. Attached at the end of this amendment is a "Version of the Amendments to the Claims with Markings to Show Changes Made."

Support for the newly added claims can be found throughout the specification. For example, support may be found on page 11, lines 8-10 and page 11, lines 25-28. Reconsideration of the application in view of the following remarks is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1, 3-8, 10-15, 17-19 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Specifically, the Examiner contends that "no evidence has been provided in the specification for successfully targeting and inhibition of glucosylceramide synthase expression in a target cell *in vitro* or *in vivo* by antisense other than using antisense targeting mRNA encoding full length glucosylceramide synthase." Applicants traverse this rejection for the arguments of record and the reasons presented below.

Section 112, first paragraph requires that the claimed invention is adequately described so as to enable the skilled artisan to make and use the invention. The instant specification teaches that either the full length antisense GCS nucleic acid sequence *or antisense GCS nucleic sequences of varying lengths* (e.g., page 11, lines 8-18) may be used in the disclosed methods and formulations. In addition, the specification teaches modifications that can be made to antisense GCS nucleic acid sequences to enhance stability, uptake and the like (e.g., page 11, lines 29-30 and page 12, lines 1-29). Thus, while the specific embodiment exemplified in the specification uses a full length antisense GCS nucleic acid sequence, the specification teaches how to make and use antisense of varying lengths, such as oligonucleotides. Applicants need not exemplify every possible claimed embodiment (e.g., antisense nucleic acids of varying lengths). In re Robins 429 F.2d 456,456-457, 166 U.S.P.Q. 556, 555 (CCPA 1970).

Moreover, applicants need not disclose every compound or species covered by the claim or an exact formula for the compound to enable one of ordinary skill in the art to make and use the compounds. In re Angstadt, 537 F. 2d 498, 190 USPQ 214 (CCPA 1976); In re Fisher, 427 F.2d 833, 166 USPQ 18 (C.C.P.A. 1970), cert. denied, 401 U.S. 956 (1971). Compounds need not be explicitly identified (i.e., specific oligonucleotides); all that is required is that sufficient guidance is provided in the specification so that one of ordinary skill may make and use the compound Petsi v. Rennhard, 363 F2d 903, 150 USPQ 669 (CCPA 1966). Applicants submit that antisense GCS nucleic acid sequences not of full length are adequately described so as to enable one of skill in the art to make and use the claimed invention. Withdrawal of this ground of rejection is respectfully requested.

In making a rejection under 35 U.S.C. § 112, the Examiner should provide

evidence that the specification fails to teach one skilled in the art to make and use the claimed invention without undue experimentation. See In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1980). The Federal Circuit has suggested factors to be considered when determining whether the amount of experimentation required is "undue," including: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See id.

Applicants invention is not undue, but rather routine for those skilled in the art. Applicants submit that the specification enables one of skill in the art to practice the invention without undue experimentation. To one of skill in the art, once a target sequence is identified, it is a matter of routine experimentation to design and screen numerous oligonucleotides for antisense activity. While potentially labor intensive, for one of skill in the art it would not constitute undue experimentation. The Federal Circuit has explicitly held that See id. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. (citing In re Angstadt, 537 f.2d 489, 502-04 (CPA 1976). Accordingly, applicants respectfully submit that any experimentation required to practice Applicants invention is not undue, but rather routine for those skilled in the art.

In addition the Examiner contends that the specification is not enabled for "the targeting and inhibition of the target glucosylceramide gene in an organism". Applicant respectfully traverses this rejection for the reasons of record and summarized herein below.

Contrary to the Examiner's contention, the specification teaches how the antisense GCS nucleic acid sequences may be introduced into a cancer cell either *in vitro* or *in vivo* (e.g., page 15, lines 15-29 and page 18, lines 23-30) and numerous cancer cells and or diseases (e.g. page 14, lines 1-20; page 15, lines 28-29 and page 16, lines 1-9) to which the instant methods and formulations may be applied. While the specific embodiment exemplified in the specification uses antisense GCS nucleic acid sequences *in vitro* in breast cancer cells, the specification teaches how to make and use the invention both *in vitro* and *in vivo* in a variety of cells. Applicants need not exemplify every possible claims embodiment (e.g., all cells, all drugs, all modes of administration). In re Robins 429 F.2d 456,456-457, 166 U.S.P.Q. 556, 555 (CCPA 1970). Applicants therefore request withdrawal of this ground of rejection.

Based on the foregoing arguments, Applicant submits that the instant disclosure provides quite sufficient information with respect to methods of for reversing drug resistance or of inducing apoptosis in cancer cells by introducing an antisense GCS nucleic acid sequence into cancer cells and formulations comprising an antisense GCS and a chemosensitizer or chemotherapeutic agent. Accordingly, Applicant respectfully submits that the Examiner has not met his burden of providing reasons or evidentiary support for the alleged non-enablement of the instant disclosure. In re Marzocchi 439 F.2d 220; 169 U.S.P.Q. 367 (CFCA 1971). Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the claims comply with 35 U.S.C. § 112 first paragraph. Accordingly, allowance is in order, and an early notification to that effect would be appreciated. Should the Examiner in reviewing the communication have any questions or need

any additional information, he is welcome to contact the undersigned at (650) 849-4902.

A fee of $445.00 (for the extension of time) is believed due. The Assistant Commissioner is hereby authorized to charge any additional fees which maybe required by this paper, or credit any overpayment to Deposit Account No. 50-1189. Docket No.: 21144706. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully, submitted,

Dated: July 18, 2001

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Version of the Amendments to the Claims with Markings to Show Changes Made

21.(New) A method for reversing drug resistance in a cancer cell, said method comprising introducing a full length antisense glucosylceramide synthase nucleic acid sequence into said cell, wherein said introduction reverses drug resistance in said cell.

22. (New) A formulation for reversing drug resistance in a cancer cell or inducing apoptosis in a cancer cell, comprising a full length antisense glucosylceramide synthase nucleic acid sequence and chemosensitizer or chemotherapeutic agent.